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liposome same (pulmonary adj2 delivery) same aeruginosa	1

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L2	L1 and pulmonary	6	L2
L1	liposome adj5 aminoglycoside	39	L1

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L3: Entry 4 of 4 File: USPT Sep 2, 1997

DOCUMENT-IDENTIFIER: US 5662929 A
TITLE: Therapeutic liposomal formulation

Brief Summary Text (13):
The encapsulation of aminoglycosides and .beta.-lactam antibiotics into liposomal formulations by the dehydration-rehydration vesicle (DRV) method has been described (Lagace et al., 1991, J. Microencapsulation 8:53-61). Disteroyl phosphatidyl-choline (DSPC) and dimyristoyl phosphatidyl-glycerol (DMPG), two synthetic phospholipids were used at a molar ratio 10:1 and at a lipid concentration of 16.5 umol/ml. The same liposomal formulation was tested "in situ" in an animal model of chronic pulmonary infection with Pseudomonas aeruginosa and permitted a marked increase of the residence time of antibiotic in lungs and a reduced systemic antibacterial agent absorption. Nevertheless, this liposomal aminoglycoside formulation did not show an improvement in the bactericidal activity as compared to free antibiotics and other controls (Omri et al., 1994, Antimicrob. Agents Chemother. 38:1090-1095). Other groups have disclosed aminoglycoside liposomal formulations (Da Cruz et al., 1993, WO 93/23015 and Proffitt et al., 1994, WO 94/12155). Nevertheless, the disclosed formulations fail to display a very drastic enhancement of the therapeutic activity of the antibiotic as compared to its activity in the free form. Indeed, the preferred aminoglycoside (netilmicin) liposomal formulation of Da Cruz et al., which comprises phosphatidylcholine (PC), cholesterol and phosphatidyl-inositol (PI), only shows a modest increase activity in vivo with the aminoglycoside as part of the liposomal formulation as compared to free aminoglycoside (at best by a factor of three). Proffitt et al., disclose a different aminoglycoside (amikacin) liposomal formulation comprising PC, cholesterol and distearoyl phosphatidylglycerol (DSPG). Although the Proffitt et al., formulation appears to be superior at enhancing the in vivo therapeutic activity of the aminoglycoside as compared to that of Da Cruz, this increase is still relatively low and dependent on the tissue (10-fold increase in spleen, 5-fold in liver and only 2-fold in lung). Importantly, the available liposomal formulations for use in treating bacterial infections do not appear to increase significantly the passage of the therapeutic agent through the bacterial membrane.

Brief Summary Text (14):
Cystic fibrosis (CF) is one of the most common lethal genetic diseases in humans. While the course of CF, varies greatly from patient to patient, it is largely determined by the degree of pulmonary involvement. In CF, deterioration appears unavoidable, and eventually leads to death. Although a CF patient prognosis has drastically improved in the second half of the century, the average survival is only 30 years of age. Of importance, a correlation between early colonization of Pseudomonas and a worse prognosis for CF patients has been observed. In addition, chronic lung infection due to Pseudomonas aeruginosa is the major cause of morbidity and mortality in patients wits cystic fibrosis (Omri et al., 1994, Antimicrob. Agents Chemother. 38:1090-1095; and Merck manual, 1992, 16th Edition, Merck Res. Lab.). In CF patients, Staphylococcus aureus, and Haemophilus influenza other Gram negative strains, are generally the early isolated pathogens. Such bacterial infections in CF patients are, in most cases, efficiently treated with antibiotics. A number of antibiotics are used for the antibacterial therapy, either

alone or in combination. The choice of a particular antibiotic regimen depends on a number of factors which include the site and severity of the infection as well as the resistance/sensitivity profile of the microorganism. Of importance is the fact that high doses of antibiotics, especially aminoglycosides, as well as long-term antibiotic treatment are often indicated in CF patients.

Brief Summary Text (48):
The mode of administration of the preparation may determine the sites and cells in the organism to which the compound will be delivered. Liposomes can be administered alone but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. The preparations may be injected parenterally, for example, intraperitoneally, intraarterially or intravenously. The preparations may also be administered via oral, subcutaneous, intramuscular and, of course, intramammary routes. For parenteral administration, they can be used, for example, in the form of a sterile aqueous solution which may contain other solutes, for example, enough salts or glucose to make the solution isotonic. Other uses, depending upon the particular properties of the preparation, may be envisioned by those skilled in the art. Delivery of the liposomal formulation by way of an aerosol is also contemplated as a preferred method of administration. For example, but not limited thereto, the formulations of the present invention could be used in the treatment of respiratory diseases. Asthma is one of the numerous diseases for which these formulations could be used.

Brief Summary Text (52):
Depending upon the desired application, the purpose of delivery, the route of delivery, the target, and other parameters relating to the use of the formulation, the size of the liposomes can be adapted according to well known methods. For example, it is well known that large liposomes are better suited for a topical application while smaller liposomes are preferred for intravenous administration. Further, the size of the liposomes affect their capacity of being phagocytized by macrophages. Thus, the size of the liposomes can be adapted in order to favor a route of administration, to favor retention in the reticulo endothelial organs or to favor phagocytosis (to treat bacteria inside the macrophage for example). The sizes of the liposomes contemplated range from the nanometer to the micron, preferably between 100 nm to 1 um. In a preferred embodiment the size of the liposomes range between approximately 200 nm to 600 nm. Such a liposomal formulation is compatible with an aerosol administration of the formulation for delivery to the lungs of an animal.

Brief Summary Text (53):
A preferred formulation includes liposomes comprising an encapsulated aminoglycoside wherein the liposomes are multilamellar vesicles having an average size ranging between 0.2 um and 0.6 um. A preferred ratio of DPPC:DMPG is about 5:1 to 20:1 and a preferred therapeutic agent to total lipid ratio is from about 1:1 to 1:10. Other preferred formulations include suitable lipids like phosphatidylcholines and or phosphatidylglycerols present individually or in mixture, in a molar ratio ranging from about 0.01 to 20. Other preferred formulations include formulations where the therapeutic agent to total lipid ratio is from 1:10 to 1:1.

Brief Summary Text (56):
A particularly important embodiment of the invention produces liposome/aminoglycoside formulation allowing a marked increased penetration of antibiotic into bacterial cells. In this embodiment the lipid mixture is dipalmitoylphosphatidylcholine (DPPC): dimirystoylphosphatidylglycerol (DMPG) at a ratio of 1:10 and 1:15, with total lipid concentration ranging from 5 to 85 mM. The final liposomal/aminoglycoside formulation had a diameter of about 0.4 uM and possessed an encapsulation efficiency of 20% and a therapeutic agent lipid ratio of 1:1. The improved bactericidal efficacy that results is related to the fact that

the therapeutic agent is not only incorporated into liposomes but is incorporated in an original combination of phospholipids that markedly improves the penetration of therapeutic agent in bacterial cells and through mucoid exopolysaccharides secreted by Pseudomonas aeruginosa.

Detailed Description Text (3):
The following examples describe analysis of liposome aminoglycoside formulations prepared as described above, wherein the aminoglycoside was tobramycin, the lipid mixture was dipalmitoylphosphatidylcholine (DPPC):dimirystoylphosphatidyiglycerol (DMPG) at a ratio of 10:1 or 15:1, with total lipid concentration ranging from 5 to 85 mM. Hydration took place with phosphate buffered saline diluted 1:20, followed by freezing at -70.degree. C. and lyophilization. Rehydration was made by adding antibiotic solution (10 mg/ml) at 1/8 portion of the initial volume, followed by filling to 50% of the initial volume with phosphate buffered saline. Liposomes were extruded first through a 1 um filter, followed by extrusion through 0.6 and 0.4 um polycarbonate membranes and centrifugation two times at 5,000.times. g for 20 min. and resuspended in PBS.

Detailed Description Text (6):
Different liposomal formulations were prepared according to Example 1 and analyzed by differential scan colorimetry. Using differential scan calorimetry, the temperatures of phase transition (T.sub.c) were calculated for the tobramycin-liposomal formulations listed in Table 1. All these formulations were then tested in vitro to assess the antibiotic kinetics of liberation from the liposomes. In addition, these formulations were tested in a non-infected mouse model as previously described (Omri et al. 1994, Antimicrob. Agents Chemother. 38:1090-1095) to assess the persistence of the liposomes in the lung. Only the DPPC/DMPG 10:1, 15:1 and DSPC. (Disteroylphosphatidylcholine)/DMPC (dimirystoylphosphatidylcholine) 15:1 liposomal formulations (shown in Table 1) exhibited the following characteristics: liberation of gradual and convenient amounts of antibiotic by virtue of their fluidity/stability characteristics. These liposomal formulations were further tested in animal model of chronic pulmonary infection to examine their antibacterial efficacy. Contrary to the two DPPC/DMPG formulations, the DSPC/DMPC formulation was shown to be inactive in this animal model. In addition, some formulations displaying a temperature of phase transition comparable to that of the two DPPC/DMPG formulations although showing the desired fluidity/stability characteristics were shown to be inefficient in the uninfected animal model. Of note, the addition of cholesterol to the formulation described in Table 1 brought the T.sub.c to a minimum value of 60.degree. C. Such formulations were incompatible with modulation of gradual antibiotic liberation and suitable interactions with bacteria. Thus, in order to maintain the desired characteristic of the liposome formulation, a low rigidity of the liposomes seems required. This low rigidity can be achieved by maintaining a low temperature of phase transition (below the body temperature of the animal to which the formulation is to be administered) and avoiding the use of cholesterol in the formulation.

Detailed Description Text (8):
Pulmonary retention of the therapeutic agent

Detailed Description Text (9):
As briefly alluded to in Example 2, studies of pulmonary retention were done with liposomes prepared with a 10:1 molar ratio of DPPC:DMPG, as prepared in Example 1, in BALB/c mice (Charles River), and using free tobramycin as control. The animals were injected intracheally as previously described (Omri et al., 1994, Antimicrob. Agents Chemother. 38:1090-1095) with one dose of 50 ul (200 ug) of the free and liposomal tobramycin preparations and lungs, kidneys and blood were collected at fixed times (Table 2). Lungs and kidneys were removed aseptically, weighed, and then homogenized in cold sterile PBS (40% [wt/vol]) for 30 s with a Polytron homogenizer. Tobramycin levels in both homogenized tissues and sera were measured by HPLC. Groups of three mice were used for each time value.

Detailed Description Text (10):
Administration of liposomal aminoglycoside formulation prepared according to this invention, resulted in a prolonged pulmonary retention time of the encapsulated form of tobramycin in lungs compared with that of the free therapeutic agent. It is to be noted, however, that the concentration of tobramycin decreases with time with the DPPC:DMPG formulation shown in Table 2. This result is in contrast to that of a DSPC:DMPG (10:1) formulation which showed a constant concentration of tobramycin over time, and hence a high stability of the liposomes (Omri et al., 1994, Antimicrob. Agents Chemother. 38:1090-1095, also see below).

Detailed Description Text (13):
To evaluate the bactericidal efficacy of a liposomal aminoglycoside formulation produced according to the present invention, male, pathogen-free, Sprague-Dawley rats weighing 175 to 225 g (Charles River) were used. Chronic infection in lungs was established by intratracheal administration of 5.times.10.sup.5 CFU of Pseudomonas aeruginosa PA 508 (mucoid phenotype) prepared in agar beads. It is to be pointed out that this rat model for chronic pulmonary infection is widely recognized as the most appropriate animal model for chronic pulmonary infections in human CF patients. After 3 days, three doses (600 ug) of free or liposome-encapsulated tobramycin were given intratracheally at intervals of 16 h. The lipid mixture were DPPC:DMPG at a molar ratio of 10:1 (formula no 1) and DPPC:DMPC at a molar ratio of 15:1 (formula no 2). Sixteen hours after the last treatment, the animals were sacrificed and the entire lungs were removed aseptically, weighed and homogenized as described previously for mice. Serial 10-fold dilutions of the homogenates in cold PBS were made and spread in triplicate on proteose peptone agar plates. Identification of P. aeruginosa was confirmed by specific cultures. CFU were counted after 24-h incubations at 37.degree. C. under 5% CO.sup.2. Counts were expressed in log CFU per pair of lungs. PBS and PBS-liposomes were used as controls. The results are listed in Table 3.

Detailed Description Text (16):
In summary the present liposomal formulations provide a very significant improvement in the delivery of therapeutic agents as compared to those previously disclosed. These formulations could be used in numerous animal systems with bacterial infections. Further, the present liposomal formulation provide a promising alternative for the treatment of chronic pulmonary infections in cystic fibrosis patients.

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cystic adj10 liposome	32

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DATE: Monday, March 26, 2007 **Purge Queries** Printable Copy Create Case

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L1	cystic same liposome same infection	146	L1

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L1: Entry 33 of 146 File: PGPB Jan 27, 2005

DOCUMENT-IDENTIFIER: US 20050019926 A1
TITLE: Compositions of nucleic acids and cationic aminoglycosides and methods of using and preparing the same

Detail Description Paragraph:
[0089] If the nucleic acid-aminoglycoside complexes are to be used in vivo, they are thus administered to a host in need of such treatment. Another variation on in vivo use is for the generation of genetic defects, e.g., transgenic or "knock-out" mice which are useful in the study of disease. An example of treatment in a patient is when a DNA construct encoding the CFTR gene is complexed with an aminoglycoside such as tobramycin (and which may be encapsulated in a liposome) as described above and combined with the target cells of a patient suffering from cystic fibrosis. In addition to the above described therapeutic effect that corrects the cystic fibrosis deficient gene, the aminoglycoside used in combination with the nucleic acid may provide further therapeutic relief, i.e., bacteriostatic or bactericidal effects, as mentioned above, in particular for the treatment of gram-negative bacterial infections in this patient population.

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L1: Entry 44 of 146 File: PGPB Jun 26, 2003

DOCUMENT-IDENTIFIER: US 20030118636 A1
TITLE: Delivery of small hydrophilic molecules packaged into lipid vesicles

Summary of Invention Paragraph:
[0025] Lipid vesicles and/or compositions of the invention including pH-sensitive proteinaceous channels may be used for pH-induced drug release. In tumors and sites of inflammation, the pH of the interstitial fluid is reduced whereas the blood flow is increased and the vasculature is "leaky." pH-sensitive liposomes have been developed for these purposes (Shi, J. Contr. Release 2002; 80:309, Drummond, Biochem. Biophys. 2000; 1463:383). The pH-sensitive proteinaceous channels of the present invention may provide release rates of drugs that are instant, i.e., within a few seconds. For example, in the lungs the pH of the airway surface liquid is reduced in subjects with inherited and acquired diseases such as cystic fibrosis and asthma as a result of lung obstruction, infection and inflammation (Coakley, J. Pancreas 2001; 2:294). Since not all lobes of the lung are affected at the same time, the use of lipid vesicles including pH-sensitive drug release channels may improve the therapeutic index of a drug administered by inhalation, wherein pathophysiological changes of the airway surface liquid, such as pH, may be used to improve inhalation therapy have not been exploited before.

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L1: Entry 45 of 146 File: PGPB May 22, 2003

DOCUMENT-IDENTIFIER: US 20030096774 A1
TITLE: Compositions of nucleic acids and cationic aminoglycosides and methods of using and preparing the same

Detail Description Paragraph:
[0089] If the nucleic acid-aminoglycoside complexes are to be used in vivo, they are thus administered to a host in need of such treatment. Another variation on in vivo use is for the generation of genetic defects, e.g., transgenic or "knock-out" mice which are useful in the study of disease. An example of treatment in a patient is when a DNA construct encoding the CFTR gene is complexed with an aminoglycoside such as tobramycin (and which may be encapsulated in a liposome) as described above and combined with the target cells of a patient suffering from cystic fibrosis. In addition to the above described therapeutic effect that corrects the cystic fibrosis deficient gene, the aminoglycoside used in combination with the nucleic acid may provide further therapeutic relief, i.e., bacteriostatic or bactericidal effects, as mentioned above, in particular for the treatment of gram-negative bacterial infections in this patient population.

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L1: Entry 134 of 146 File: USPT Jan 12, 1999

DOCUMENT-IDENTIFIER: US 5858784 A
TITLE: Expression of cloned genes in the lung by aerosol- and liposome-based delivery

Detailed Description Text (49):
In general, in the treatment of cancer, it will usually be necessary to administer sequential doses at intervals ranging from every 8 to 12 hours to once a month, until significant amelioration or complete disappearance of the cancer results, or until dose limiting host toxicity develops. Similar administration protocols may also be used in e.g. patients where all macroscopic evidence of tumor has been removed, in order to prevent tumor recurrence due to persistence of undetected microscopic disease. To treat pulmonary infections such as bronchitis and pneumonia, it will usually be necessary to administer at least one dose per day over a period of about 4 to about 21 consecutive days or longer. The treatment is usually carried out on consecutive days because new areas of the lungs open up to penetration and deposition of the nucleic acid with increasing resolution of the infection. The success of the treatment can be monitored and the administration regimen altered by assessing conventional clinical criteria; e.g., clearing of radiographic infiltrate, improved arterial PO.sub.2 (e.g., >70 mmHg), reduction in dyspnea, respiratory rate and/or fever. For the treatment of genetic disorders, such as cystic fibrosis, the liposome-nucleic acid complex will be administered at regular intervals, from once a week to once every one to several months, in order to replace the normal CRTR protein in critical host airway cells, since these cells continue to turn over. It may also be possible to stably transfect the CMTR gene into appropriate lung stem cells, which would then provide a continuous source of normal airway cells without requiring lifelong treatment. Potential therapeutic effects of the gene product can be measured, by determining the effects of gene expression on survival of transgenic host mammals in which the transgene is expressed. Production of significant amounts of a transgene product will substantially prolong the survival of the affiliated host.

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